Prospective CT Screening for Lung Cancer in a High-Risk Population

HIV-Positive Smokers

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Background: Epidemiological evidence suggests that HIV-infected individuals are at increased risk of lung cancer, but no data exist because large computed tomography (CT) screening trials routinely exclude HIV-infected participants.

Methods: From 2006 to 2013, we conducted the world's first lung cancer screening trial of 224 HIV-infected current/former smokers to assess the CT detection rates of lung cancer. We also used 130 HIV-infected patients with known lung cancer to determine radiographic markers of lung cancer risk using multivariate analysis.

Results: Median age was 48 years with 34 pack-years smoked. During 678 person-years, one lung cancer was found on incident screening. Besides this lung cancer case, 18 deaths (8%) occurred, but none were cancer related. There were no interim diagnoses of lung or extrapulmonary cancers. None of the pulmonary nodules detected in 48 participants at baseline were diagnosed as cancer by study end. The heterogeneity of emphysema across the entire lung as measured by CT densitometry was significantly higher in HIV-infected subjects with lung cancer compared with the heterogeneity of emphysema in those without HIV ($p \leq 0.01$). On multivariate regression analysis, increased age, higher smoking pack-years, low CD4 nadir, and increased heterogeneity of emphysema on quantitative CT imaging were all significantly associated with lung cancer.

Conclusions: Despite a high rate of active smoking among HIV-infected participants, only one lung cancer was detected in 678 patient-years. This was probably because of the young age of participants suggesting that CT screening of high-risk populations should strongly consider advanced age as a critical inclusion criterion. Future screening trials in urban American must also incorporate robust measures to ensure HIV patient compliance, adherence, and smoking cessation.

Key Words: HIV, Lung cancer, Computed tomography screening, Lung cancer screening, High-risk populations.

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HIV-infected smokers are reported to have a higher relative risk of developing lung cancer compared with that in the general population, and lung cancer has emerged as the most common and fatal non–AIDS-associated malignancy in most western nations.[1–10] After controlling for cigarette smoking, the best epidemiological estimates are that HIV infection increases lung cancer risk by 2.5-fold.[11–14] Because lung cancer increases markedly with age and duration of smoking, lung cancer may become more common and account for even more deaths as HIV-infected patients live longer with highly active antiretroviral therapy (ART).

The high case fatality rate in HIV-associated lung cancer has been shown not to be attributable to HIV-related causes, but instead, is primarily attributed to an advanced stage of lung cancer presentation in HIV patients.[15,16] Late lung cancer diagnoses occur even in HIV specialty clinics where frequent chest radiographs evaluating opportunistic pulmonary infections fail to detect lung cancer early.[15,17] In fact, approximately 130 HIV-infected lung cancer patients have presented to our institution with more than 80% having late-stage disease.[15]

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Since the 1990s, computed tomography (CT) has been explored as an early detection strategy for lung cancer[18–22] with suggestions that it may allow early-stage diagnosis and definitive treatment.[23,37] The National Lung Cancer CT Screening Trial (NLST) reported a 20% reduction in mortality associated with annual CT screening for older, heavy smokers at high risk for lung cancer.[24] Given the current late stage of presentation of HIV-associated lung cancer, CT screening may have profound implications for improving earlier diagnosis of this high-risk group of patients. There are no data, however, to support routine lung cancer screening in HIV-infected smokers because most CT screening studies, including the NLST, excluded their enrollment.

Given that no HIV-infected subjects were enrolled in the NLST, the late-stage presentation of HIV-associated lung cancer, and the epidemiological evidence suggesting this population was at particularly high risk for lung cancer, we hypothesized that annual CT screening in HIV-infected smokers may improve early lung cancer detection. From 2006 to 2013, we initiated a single-armed, prospective, observational study assessing the incidence and stage at diagnosis of lung cancer among HIV-infected smokers undergoing annual CT screening. The primary objective was to determine the prevalence and incidence of lung cancer in HIV-infected smokers. Our secondary objectives were to evaluate the feasibility and adherence to intensive screening in this population, to examine rates of false-positive nodule detection, to determine whether CT screening could change the stage distribution of HIV-associated cancer to that of an early-stage disease, and to determine radiographic markers that may differentiate between HIV-infected smokers with and without lung cancer.

PATIENTS AND METHODS

Participants

From January 2006 through May 2013, HIV-infected smokers were recruited and followed from HIV outpatient clinics throughout Baltimore City and from the AIDS Linked to the Intra-Venous Experience cohort at Johns Hopkins.[9] The study was approved by the Johns Hopkins Institutional Review Board, and all subjects provided informed consent. Eligible participants were seropositive for HIV by enzyme-linked immunosorbent assay, had no symptoms of a lung malignancy, aged 25 years or older, and current or former smokers (quit within 15 years) with 20 pack-years of use or more. Exclusion criteria included chest CT examination 18 months before eligibility, pregnancy, history of lung cancer, active respiratory infection, or prior cytotoxic therapy within 6 months. A total of 236 participants were registered. Twelve subjects were excluded because of a CT scan within 18 months of registration leaving 224 participants. Forty-nine participants from the AIDS Linked to the Intra-Venous Experience study were registered from 2010 to 2011 and consented to undergo baseline and end of study imaging only. All enrolled subjects were unselected, and no preference was given toward recruiting "healthier" smokers.

Patient navigators tracked all study appointments, including contacting subjects before appointments, providing minimal financial remuneration for attendance at each visit, and coordinating follow-up study visits with routine clinical care.

Screening

At baseline, smoking habits, general health, occupational, and contact data were recorded, and portable spirometry was performed. Forced vital capacity and forced expiratory volume in 1 second were measured at each CT screening. Participants were to have a low-dose helical CT scan at baseline (T0) and up to four scans annually (T1–T4). CT screenings were without contrast using a low-dose regimen (120 kVp, 50–200 mA, 1–5 mm axial reconstruction, 1.1 pitch with collimation of 64 × 0.6 mm) on a single multidetector scanner (SOMATOM 64; Siemens Medical Solutions, Erlangen, Germany) with daily calibration. Each CT was read independently by two radiologists with interobserver variability ameliorated through joint discussion. Due to previous work in evaluating CT changes in HIV patients, we presumed that CT screening would yield a high incidence of inflammatory nodules and scarring from previous pulmonary infections in HIV-positive patients.[25] Our protocol thus differed from the current, robust protocols of International Early Lung Cancer Action Project (I ELCAP) [26] and the National Comprehensive Cancer Network (NCCN) for CT screening[27] in allowing our radiologists to assess noncalcified pulmonary nodules of 4 to 9 mm diameter as suspicious or nonsuspicious on an individual basis. Repeat low-dose helical CT was recommended at 3 or 6 months for suspicious nodules such as enlarging nodules less than 7 mm diameter or those with other suspicious changes. For nodules 10 mm in diameter or more or enlarging nodules more than 7 mm in diameter, additional diagnostic tests could include CT screening at 3 or 6 months, fluorodeoxyglucose (FDG)-positron emission tomography or Technetium-99m depreotide scintigraphy, or biopsy (percutaneous, bronchoscopic, thoracoscopic, or open biopsy).

Vital Status

Participants were contacted semiannually enabling updates on health status, contact information, and smoking behavior. The social security numbers of those lost to follow-up were cross referenced with the Social Security Death Index to ascertain vital status. Cause of death was abstracted from the medical record. Data on current CD4 cell count, nadir CD4 count, HIV viral load, and HIV ART were obtained from patients, their health care provider, and from medical records.

CT Densitometry of Screening Participants

CT scans were analyzed for emphysema using Pulmonary Workstation 2.0 software (Vida Diagnosis, Iowa City, IA). The program determines lung volumes and histogram statistics of all lung pixel attenuation values. Extent of emphysema was estimated by quantifying the percentage of voxels having an attenuation value lower than −910 Hounsfield units (HUs). This threshold was chosen empirically because of the thickness of the CT scans in this study and was validated by analyzing several CT scans over a range of HUs (from −910 to −1040 HU) in 10-HU increments. All lung densitometry measurements were corrected by normalizing to the lung air volume being considered. Of the 224 baseline

scans available, 117 were able to be used for CT densitometry calculations. Two investigators independently performed these analyses with any discrepancies resolved by committee.

CT Densitometry of HIV-Infected Lung Cancer Patients

From 1989 to 2012 at the Johns Hopkins Hospital, 130 HIV-infected patients were diagnosed with lung cancer. From these patients, 39 had available archived chest CT scan digital data that could be analyzed quantitatively.

Statistical Analysis

Comparisons of continuous and dichotomous variables between groups were performed with the Student's *t* test (two-tailed) and χ^2 tests, respectively. Multivariable logistic regression models estimated odds ratios with 95% confidence intervals and were considered significant for *p* values less than 0.05. Statistical analyses were performed with STATA software (Stata Corporation, College Station, TX).

RESULTS

Participant Characteristics

We recruited 224 asymptomatic HIV smokers for CT screening (Table 1). At study entry, the median age was 48 years, 90% were black, and 58% had a history of injecting drugs. Most were current smokers (89%) with a median of 34 pack-years smoked. Most had previously received ART. These 224 screened participants were dissimilar demographically to 130 HIV-associated lung cancer patients previously diagnosed at our institution, with the latter being more immunocompromised with higher viral counts and having more obstructive lung disease (Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/JTO/A560). The age distribution of the screened participants has a bimodal, normal age distribution around a median of 48 years old (Supplementary Figure 1, Supplementary Digital Content 2, http://links.lww.com/JTO/A561).

TABLE 1. Baseline Characteristics of HIV-Infected Individuals enrolled in the Lung Cancer Detection by CT Screening Study (N = 224)

Characteristics	No. of Subjects (%)
Age, median [IQR], yr	48 [44–53]
Sex (M/F)	161/63
Race	
Blacks	201 (90)
Whites	22 (10)
Hispanic or Latino	1 (0.5)
Smoking status	
Former	25 (11)
Current	199 (89)
Never	0 (0)
Pack-years smoked, median [IQR], yr	34 [31–36]
History of marijuana use	90 (40)
History of cocaine use	65 (29)
IVDU (*n* = 222)	129 (58)
Hepatitis C (*n* = 213)	114 (54)
TB skin-test positive (*n* = 210)	44 (21)
STD (*n* = 189)	84 (44)
AZT (*n* = 209)	143 (68)
CD4 nadir, median [IQR], cells per cubic millimeter (*n* = 200)	179 [61–332]
CD4 cell count, median [IQR], cells per cubic millimeter (*n* = 187)	400 [217–568]
Viral load <400 cells per cubic millimeter (*n* = 207)	123 (59.1)
FEV1, median [IQR],% predicted	85 [70–101]
FVC, median [IQR], % predicted	88 [74–101]
FEV1/FVC, median [IQR],	81 [73–91]
Highest educational level attained (*n* = 126)	
Middle school	65 (52)
High school	40 (32)
College degree	21 (17)
Annual income (*n* = 87)	
<$8,000	63 (72)
$8,000 to $14,999	12 (14)
$15,000 to $24,999	10 (12)
$25,000 to $49,999	2 (3)

Some subjects had missing demographic data as noted.

IQR, interquartile range; IVDU, intravenous venous drug user; TB, tuberculosis; STD, sexually transmitted disease; AZT, azidothymidine; CT, computed tomography; FEV1, forced expiratory volume in 1 second; FEV1/FVC, percentage of the vital capacity which is expired in the first second of maximal expiration.

Adherence to Screening

More than 70% of those eligible patients received both a baseline CT scan and a CT scan in the final year of the study (Fig. 1).The total length of follow-up was 678 patient-years with the median length of follow-up being 3.2 years. After baseline scanning, 44% of eligible patients received a T1 scan, 46% had a T2 scan, 68% received a T3 scan, and fully 71% returned for a final T4 scan (Fig. 1). Participation in each annual screening was hindered by regular changes in residence and frequent alterations in contact information. Of five possible scans for all 224 participants, 18 (8%) received only one scan, 103 (46%) had two scans, 44 (20%) had three scans, 39 (17%) had four scans, and 20 (9%) received all five scans.

Screening Results

Forty-eight nodules, 32 at baseline and 16 during incident screening, were detected during the study period and followed (Supplementary Table 2, Supplementary Digital Content 1, http://links.lww.com/JTO/A560). The majority of the 48 nodules were solid; ground-glass consistency represented approximately 30%. Only 25% of nodules were larger than 1 cm in diameter (Supplementary Table 3, Supplementary Digital Content 1, http://links.lww.com/JTO/A560). None of these nodules were found to be malignant during subsequent examinations. Of the 48 nodules, 38 were judged not to be suspicious by the radiologists. These included 14 of 38 thought to be caused by chronic inflammation such as from fungal or granulomatous disease, whereas 24 of 38 were thought to have noninflammatory causes such as active infection, scarring

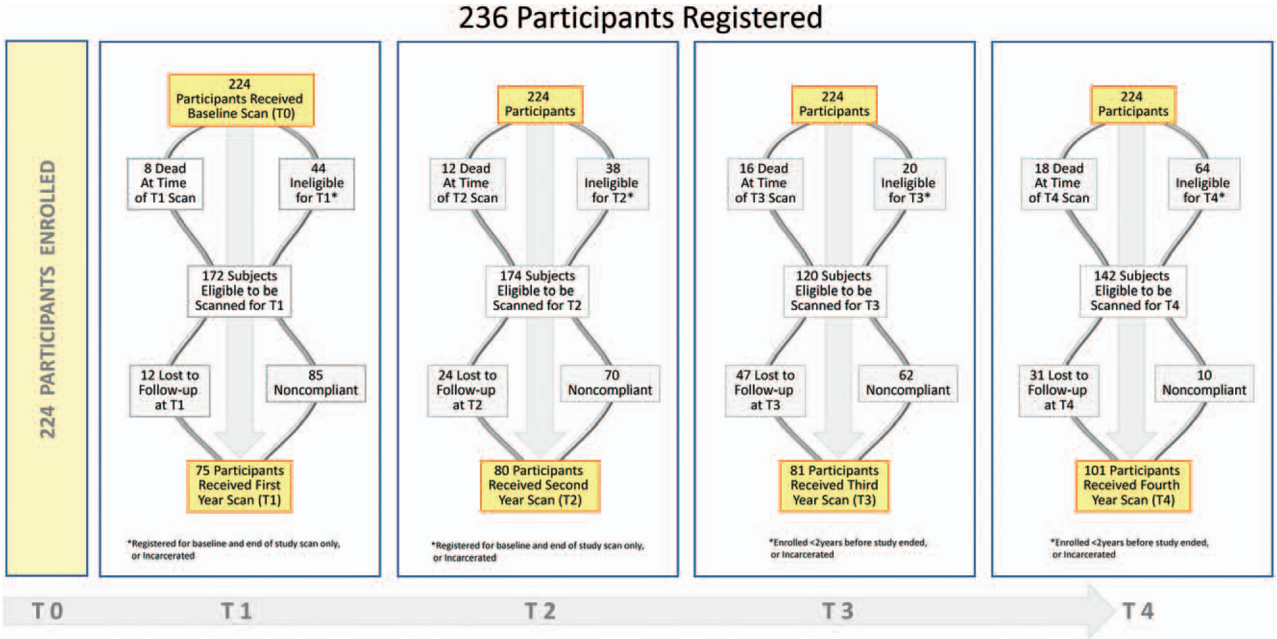

FIGURE 1. Flow chart of registered and enrolled HIV smokers. Flow diagram of HIV smokers enrolled in the lung cancer screening study by year of study participation.

from previous infection, or hamartomas. Ten participants with suspicious nodules underwent further CT imaging. Two received a positron emission tomography scan, and only one had a bronchoscopic biopsy. No participant received surgery caused by a false-positive screening.

Although no subject had an interim diagnosis of lung cancer, one non–small-cell carcinoma (NSCLC) of advanced staged (stage 3B) was detected on incident, first-year screening after baseline. The baseline screening CT scan of this patient was at the time not thought to be clinically significant, because the image showed mild hilar adenopathy typical of HIV patients. But, by the time of the first annual T1 screening, there was clear evidence of interval growth in this patient's hilar mass. The patient elected not to have treatment and died 4 months after diagnosis. There were 18 other deaths; all due to causes other than lung cancer. Sixteen of these patients had known CD4 counts at the time of death with 40% (7 of 16) of the patients having a CD4 less than 200 cells per cubic millimeter. Of these seven participants, three died of pneumonia and respiratory failure, two of cancer (tonsillar and pancreatic), and one of encephalitis and renal failure, each."

Incidental Findings

Of the 224 patients with T0 imaging, 189 participants (84%) had incidental abnormal intrathoracic findings other than suspicious pulmonary nodules. The most often observed intrathoracic abnormalities were emphysematous changes in 69 (37%), pneumonia in 69 (37%), and CT evidence of coronary artery disease in 58 (31%) participants (Supplementary Table 4, Supplementary Digital Content 1, http://links.lww.com/JTO/A560). Extrathoracic disease was evident in 40% of patients with the majority being renal and hepatic abnormalities. There was a low prevalence of incidental findings that prompted further investigations in the chest and abdomen occurring in 1% and 7%, respectively. Moreover, no extrapulmonary lesions suspicious for cancer were identified.

CT Densitometry

Given the high rate of emphysema detected incidentally and emphysema's high predictive value for lung cancer, we performed CT densitometry analyses of HIV-infected subjects with and without lung cancer. Of the 224 HIV-infected subjects with baseline CT scans, 117 (all without lung cancer) had scans suitable for densitometry. Densitometry analyses of the 117 scans from the CT screening study were compared with 39 scans from HIV-infected patients with known lung cancer diagnosed at our institution. These two groups were dissimilar in age, smoking, the use of azidothymidine, and pulmonary function tests (Supplementary Table 5, Supplementary Digital Content 1, http://links.lww.com/JTO/A560).

To assess the degree of heterogeneity of bilateral emphysematous changes in these patients, we measured the variability in voxel intensity across both lung fields in those with and without cancer. The SD of voxel intensity, corrected for lung air volume, was significantly higher in those HIV subjects with lung cancer versus those without lung cancer ($p = 0.0001$; Fig. 2).

Because decreased innate immunity has been associated with emphysema both preclinically and clinically,[28,29] we investigated whether there were differences in the association of nadir CD4 counts and CT densitometry changes in HIV-infected subjects with and without lung cancer. With lower nadir CD4 counts in HIV subjects with lung cancer, there was a significant increase in emphysematous changes by CT densitometric scoring ($p < 0.001$; Fig. 3). This inverse

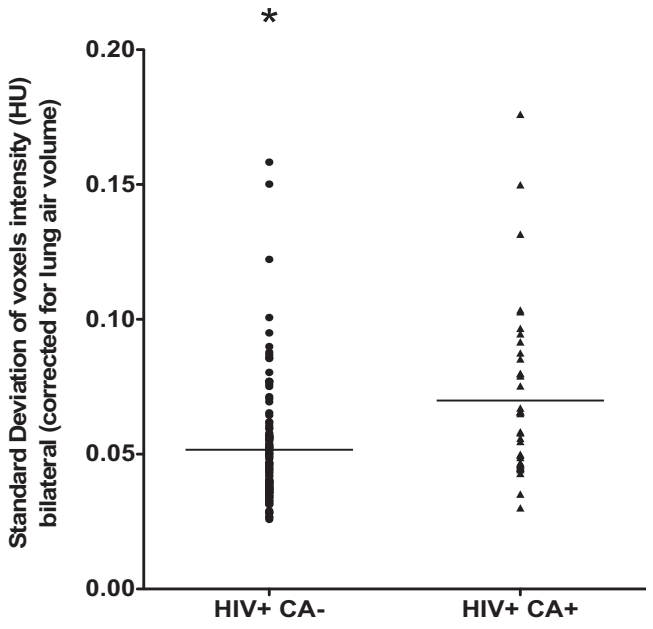

FIGURE 2. Heterogeneity of emphysema of 39 HIV-infected patients with lung cancer and 117 HIV-infected smokers without lung cancer as measured by the variability (SD) in voxel intensities, corrected for lung air volume. The SD was significantly higher in those HIV subjects with lung cancer versus those without lung cancer ($p = 0.0001$).

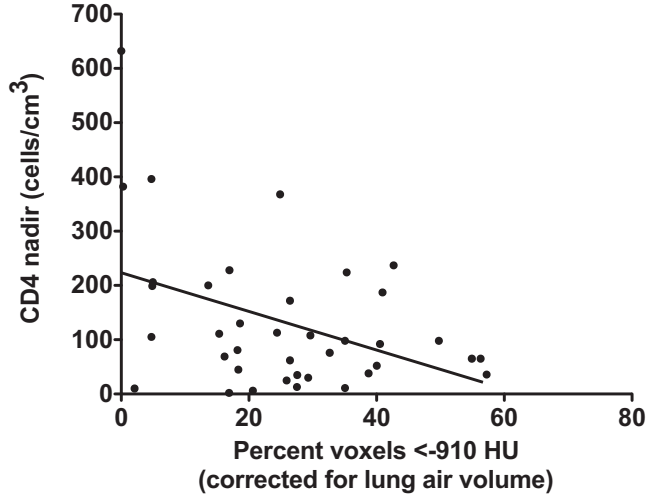

FIGURE 3. Inverse correlation between CD4 counts in cells per cubic millimeter and the percentage of voxels with attenuation less than –910 HU (corrected for lung air volume) in 38 HIV-infected patients with lung cancer. Only one HIV-infected individual with lung cancer had a CD4 count >400 cells per cubic millimeter.

correlation was not observed in HIV subjects without lung cancer ($p = 0.25$). Moreover, because only one HIV patient with lung cancer of 39 patients had a nadir CD4 count more than 400 cells per cubic millimeter, the threshold of nadir CD4 may represent a clinical biomarker to identify HIV smokers at increased risk for lung cancer.

TABLE 2. Adjusted Odds Ratio in 140 HIV Individuals (117 HIV-Positive Smokers and 39 HIV-Positive Lung Cancer Patients) of Having Lung Cancer Based on Clinical and Radiographic Characteristics

	Odds Ratio	95% Confidence Interval	*p* Value
Clinical characteristics			
Increasing age	1.08	1.01–1.15	0.02
Increasing pack-years	1.09	1.04–1.15	<0.0001
Decreasing CD4 nadir	1.006	1.002–1.01	0.006
Increased SD/TLV	1.23	1.03–1.47	0.02

Logistic regression model includes subjects' age in years, pack-years cigarette smoking history, CD4 nadir counts (continuous), SD/TLV (SD of voxel intensities corrected by total bilateral lung air volumes), and the percentage of voxels less than −910 Hounsfield units corrected by total lung volume.

Using our 117 HIV-positive patients from our screening cohort and our 39 known HIV-positive lung cancer patients, we performed a multivariate logistic regression analysis assessing clinical and radiographic risk factors associated with lung cancer in HIV-infected patients. Increased age, higher pack-years of cigarette smoking, low CD4 count nadir, and increased heterogeneity of emphysema on CT imaging were all significantly associated with lung cancer in HIV patients (Table 2).

DISCUSSION

This observational study is the first to evaluate CT screening for lung cancer in HIV smokers. Despite 89% of our cohort being active smokers and the epidemiological evidence of a twofold increase in lung cancer incidence in HIV-infected versus non–HIV-infected individuals,[1–9,30–34] we found only one incident cancer during 678 patient-years using up to five annual CT screenings. Even with the limitation of a small sample size, this is a low rate of lung cancer detection despite our appropriate targeting of a community, epidemiologically, at high risk for lung cancer.[35–41] Although selection bias in recruiting "healthier" HIV smokers is a remote possibility, the more plausible explanation for this low detection rate is the cohort's young median age of 48 years. The normal, Gaussian age distribution shows that this recruitment around a median age of 48 years old most likely reflects the range of ages of HIV-positive patients who sought care at our outpatient clinics and does not suggest selection bias in recruitment. We mistakenly hypothesized that the low immunosurveillance associated with HIV infection would be the most powerful risk factor for lung cancer in our cohort and underestimated the significant contribution of advanced age as a risk factor. In 2003, when our trial was initially designed, the median patient age of all HIV-positive patients in our HIV outpatient clinic was 42.4 years. In 2013, with the widespread use of ART, the median age of all outpatient HIV-positive patients has increased to 52.9 years. Indeed, in most CT screening trials involving non-HIV subjects, 55 years old is the minimum age of eligibility for study participation, and in the original I ELCAP CT screening study published in 1999 by Henschke et al.[36] which showed a 2.7% prevalent lung cancer detection

rate, the 1000 participants had a median age of 67 years. Prospective cohort studies have also shown a strong association between advanced age and increased risk of lung cancer in HIV-infected subjects.[42] The low rate of HIV-infected lung cancer in this trial supports the null hypothesis, and the importance of advanced age to lung cancer incidence, even in communities at high risk for lung cancer. As more CT screening programs increasingly develop algorithms to target high-risk populations of smokers, our negative study suggests that the contribution of advanced age as a significant risk factor should not be ignored.

We found that noncalcified nodules 4 mm in diameter or more were common in smokers who were HIV positive, with the majority of them (38 of 48) interpreted as nonsuspicious by our radiologists due to active infection such as tuberculosis and pneumonia, scarring from previous infection, or granulomatous disease. Only 10 of 48 nodules were thought to be suspicious by the radiologists and all participants with these nodules returned for subsequent imaging. These subsequent images all showed definitively that the lesions were not malignant, sometimes even showing nodule regression.

More than 80% of the screened cohort had additional intrathoracic CT abnormalities, including a third with diffuse coronary artery disease, a finding noted previously.[43] Similar to CT screening trials in non-HIV patients, however, incidental abnormalities requiring further diagnostic work-up were few.[44] Such a high rate of additional intrathoracic findings is an interesting observation as it begs the question whether abnormal CT changes in an HIV-positive and HIV-negative patient require similar follow-up, or whether HIV-positive patients on ART have medication-induced changes to the lung and other organs that are new entities which may raise the false-positive rate and cause potential harm to the patient if aggressively pursued.

But, the most frequently observed intrathoracic abnormalities were emphysematous changes to the lung parenchyma. We endeavored to quantify these emphysematous abnormalities to assess whether they may prove to differentiate in an even higher risk subpopulation of HIV smokers. We did this by comparing 117 participants from our CT screening study with 39 HIV-positive lung cancer patients with CT scans who had previously been diagnosed at Johns Hopkins. There is a suggested association between bullous disease and cannabis usage,[45] but the causal link is not established.[46] In this study, however, there was no difference in the cannabis usage between the 117 participants and the 39 HIV-positive lung cancer patients. Interestingly, there was a significant correlation between decreasing nadir CD4 counts and increasing degrees of CT-determined emphysema in those with lung cancer. Because only one HIV patient with lung cancer had a nadir CD4 count more than 400 cells per cubic millimeter, our data suggest that a certain threshold of nadir CD4 counts for CT screening eligibility may target those HIV smokers at particularly high risk for emphysema-mediated CT densitometry changes. This could also be explained, however, by the possibility that our lung cancer patients with HIV, who were older and smoked more, may have presented for care later from an immune standpoint, with delayed use of ART. However, an increasingly robust literature suggests the significant dose–response relation of decreasing HIV-induced immunity, often measured by CD4 counts, and the increasing risk of non–AIDS-defining malignancies.[47–49] Finally, our multivariate analysis, between the 39 patients with lung cancer previously diagnosed at Johns Hopkins and those 117 patients without the disease from our screening study, also identified low CD4 nadir as a risk factor for lung cancer, along with increased age, higher pack-years cigarette smoking, and an enhanced heterogeneous pattern of emphysema on CT scanning. Injury and inflammation are known to be pivotal in the nonuniformity of emphysema in the lung,[50] and a dysfunctional immune response in HIV subjects may have accentuated the upper lobe–predominant emphysema observed in HIV subjects.

Despite patient navigators and remuneration for continued participation, this study is limited by few eligible subjects returning for all five scans. Longitudinal engagement in regular HIV care in U.S. urban settings also is a limitation to effective antiretroviral treatment.[51] A recent report of 22,984 adult HIV outpatients receiving care in the United States between 2001 to 2009 indicated that only 20.4% of HIV outpatients were retained as patients on a continual basis without interruption or loss to follow-up.[52] Urban HIV cohorts with a high prevalence of polysubstance abuse are especially vulnerable to poor compliance and follow-up rates.[53,54] Many of our participants returned for a final CT screening at study's end with more than 70% of eligible HIV subjects completing at least a baseline and final CT scan. This suggests that only 14% of our original cohort were truly lost to follow-up, and the majority of participants were merely grossly noncompliant.

Because only one lung cancer was detected, we were unable to investigate the secondary endpoint concerning whether CT screening changes the stage distribution of NSCLC in screened HIV patients versus historic controls. The NLST suggests that stage distribution may change in non-HIV individuals, but the aggressiveness of NSCLC in the HIV-infected patient makes this an open question.

Given the results of this pilot screening study, considerable thought must be given concerning the execution of any large screening study in this high-risk population especially given the many other factors that could make a case against lung cancer screening in such persons; such as "over diagnosis bias,"[55]competing mortality over a course of screening, more aggressive cancer types, faster interval progression of cancers, and the personal anxiety, financial burden, and the morbidity because of the work-up of false-positive tests. At the very minimum, we believe that until the median age of HIV smokers increases, the rate of detection by helical CT of HIV-associated lung cancers will remain low. Advanced age and length of exposure to cigarette smoking are strong risk factors for lung cancer, and most CT screening studies use age older than 55 years as an important eligibility criterion. Our identification of biologic and radiographic markers in HIV smokers to define an even higher subpopulation of high-risk individuals may allow algorithms to determine lung cancer risk more effectively, individualize the frequency of

subsequent scans, reduce false positives, and limit the costs of future lung cancer screening trials. Given the high rate of active smokers in an HIV community and the epidemiological data, as the median age of HIV-infected individuals surpasses 55 years in the United States, perhaps a far larger study enrolling older HIV-positive smokers may answer some of the initial questions we raised here. However, for such a study to be feasible in an urban American HIV cohort plagued by polysubstance abuse, considerable measures to ensure patient compliance, adherence, and smoking cessation must also ensue.

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